REMARKS

Claims are1-88 are pending as of the mailing date of the Office Action. The Examiner made the restriction requirement final and withdrew claims 1-34, 41, 55, 69, 80, and 88 as drawn to a nonelected invention. Thus, claims 35-40, 42-54, 56-68, 70-79, and 81-87 are under examination. Regarding the election requirement, the Examiner indicated that she will examine the conjugate group "lipids," which includes cholesterol. Claims 39, 53, 67, 78, and 87 have been amended to limit the conjugate to "lipids." Support for the amendment can be found, for example, in the claims as filed.

Claim Objections

The Examiner objected to claims 39, 53, 67, 78, and 87 as drawn to non-elected conjugate groups and requested correction. Applicants have amended claims 39, 53, 67, 78, and 87 to limit conjugates to "lipids." Applicants make the amendment without disclaimer and reserve the right to pursue non-elected conjugates in one or more continuation and/or divisional applications.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejected claims 75-77, 81, and 83-86 as allegedly anticipated by U.S. Patent No. 5,998,203 to Matulic-Adamic *et al.* (Matulic), asserting that Matulic discloses a ribozyme that meets the structural limitations of a dsRNA, has modifications to promote stability (including phosphorothioate modifications and 2' modifications), is complementary to a target sequence, and can cleave target RNA to inhibit gene expression. The Examiner argued that this ribozyme inherently induces RNA interference.

The Examiner also rejected claims 75, 76, 78, 79, 81, and 83-86 as allegedly anticipated by WO 94/01550 by Agrawal *et al.* (Agrawal). The Examiner asserted that Agrawal teaches dsRNAs having modified bases and/or sugars and cholesteryl or other lipophilic groups, phsophorothioates, 2'-O-methyl modifications, and overhangs.

Applicants respectfully disagree with the Examiner and traverse each anticipation rejection.

Applicants submit that neither Matulic nor Agrawal anticipate the presently pending claims. Anticipation requires that a single reference disclose each and every element of the claim, *W.L. Gore & Assocs. v. Garlock*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984), explicitly or inherently, and that the reference must disclose the elements arranged as in the claim, *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984). Applicants submit that neither of the cited references anticipates the present claims, because neither reference discloses each and every element of the present claims.

First, Matulic does not disclose each and every element of the rejected claims, as arranged in the claims. Matulic discloses ribozymes having 5'- and/or 3'-caps (see, for example, Matulic at col. 3, line 4 – col. 4, line 30; and col. 9, lines 46-49) of defined structures (see, *id.*), as well as certain "prior art" ribozymes having at least one double stranded portion (see, for example, Matulic at Fig. 3). However, Matulic does not disclose a double stranded polynucleotide comprising a sense strand, an antisense strand, and a conjugate, wherein the sense and/or antisense strand comprises at least one 2' modified nucleotide, and thus the Examiner has not set forth a *prima facie* case for anticipation. More precisely, the Examiner has not indicated where in Matulic the structure of helix 4 in Fig. 3 is described as comprising a sense and antisense strand. Also, the Examiner has not indicated where Matulic discloses a conjugate in combination with the structure of Fig. 3 or in combination with the structures disclosed in column 3. Because Matulic does not disclose each and every element of the rejected claims, as arranged in the claims, Matulic does not anticipate the rejected claims. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on Matulic.

Second, Agrawal also does not disclose each and every element of the rejected claims as arranged in the claims. Agrawal discloses oligonucleotides having self-complementary regions for antisense therapeutic approaches as a means of rendering an

antisense oligonucleotide resistant to nucleolytic degradation (see, for example, page 5, lines 17-22; page 5, lines 1-33; page 6, lines 10-18). Further, Agrawal discloses separate "target hybridizing" and "self-complementary" regions (see, for example, page 8 at lines 22-24, and Fig. 1) in the antisense oligonucleotide, wherein the "self-complementary region is less thermodynamically stable than the intermolecular base pairing between the target hybridizing region and a complementary oligonucleotide" (see page 29, lines 5-10; see also page 29, line 5 to page 30, line 10). However, Agrawal does not disclose a double stranded polynucleotide comprising a sense strand, an antisense strand, and a conjugate, wherein the sense and/or the antisense strand comprises at least one 2' modified oligonucleotide. Further, the rejected claims do not recite a polynucleotide subject to the thermodynamic stability requirements specifically enumerated in Agrawal, nor do the rejected claims require overlapping "target hybridizing" and "self-complementary" regions as enumerated in Agrawal. Because Agrawal does not disclose each and every element of the rejected claims, as arranged in the claims, Agrawal does not anticipate the rejected claims. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on Agrawal.

Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected claims 35-40, 42-54, 56-58, 70-79, and 81-87 as allegedly obvious in light of the following references:

- Amarzguioui *et al.* (2003) Tolerance for mutations and chemical modifications in a siRNA, *Nucleic Acids Res.* 31/2:589-595, (Amarzguioui);
- Parrish *et al.* (2000) Functional Anatomy of a dsRNA Trigger: Differential Requirement for the Two Trigger Strands in RNA Interference, *Molecular Cell* 6:1077-1087, (Parrish);
- Elbashir *et al.* (2001) RNA interference is mediated by 21- and 22-nucleotide RNAs, *Genes & Development* 15:188-200, (Elbashir);
- U.S. Patent No. 6,111,086 to Scaringe, (Scaringe);
- U.S. Patent Application 2004/0009938 by Manoharan *et al.*, (Manoharan);

- Letsinger *et al.* (1989) Cholesteryl-conjugated oligonucleotides: Synthesis, properties, and activity as inhibitors of replication of human immunodeficiency virus in cell culture, *Proc. Natl. Acad. Sci. USA*86:6553-6556, (Letsinger); and
- WO 02/094185 in the name of Beigelman *et al.*, (Beigelman).

First, the Examiner asserted that Amarzguioui teaches 19- and 21-mer siRNA duplexes and RNAi, wherein the siRNA comprise 2'-O-methyl, 2'-O-allyl or phosphorothioates for increased silencing persistence at the 5' and 3' ends and in 3' overhangs, and argued that Elbashir discloses that overhangs increase efficiency of target RNA cleavage. She conceded that Amarzguioui does not teach orthoester modifications, cholesterol conjugates, or fluorine-modified nucleotides, but asserted that Parrish teaches modified siRNA duplexes and RNAi, including 2'-O-alkyl modifications at various nucleotide positions of the duplex, as well as 2'-fluorouracil. The Examiner argued that Scaringe teaches orthoester protecting groups and their use with oligonucleotides and ribozymes, and that orthoester groups alone or in combination with 2' modifications help minimize degradation. The Examiner also argued that Beigelman teaches lipid conjugates of siRNAs, and cited Manoharan and Letsinger for the proposition that cholesterol is an ideal selection for a lipid conjugate, stating that Beigelman teaches conjugates that improve bioavailability and pharmacodynamics.

Finally, the Examiner asserted that it would have been obvious to use a fluorine modification as taught by Parrish and Beigelman, an orthoester as taught by Scaringe, and a lipid conjugate as taught by Beigelman to improve pharmacodynamics, enhance stability, and minimize degradation with a reasonable expectation of success since the cited modifications were known in the art.

Applicants respectfully disagree with the Examiner and traverse each of the obviousness rejections.

An obviousness determination requires the Examiner to view the claimed invention as a whole, such that "an artisan of ordinary skill in the art at the time of invention ... would have selected the various elements from the prior art and combined

them in the claimed manner." *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, *5 (Fed. Cir. 2005), citing *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270 (Fed. Cir. 2004). It is improper to "import hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components." *Id.* at *4. "[S]ection 103 requires that there be some suggestion or motivation, before the invention itself, to make the new combination." *Id.*, at *5, quoting *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). "Simply identifying all of the elements in a claim in the prior art does not render a claim obvious." *Princeton*, at *6. Applicants submit that under these standards the cited references do not render the rejected claims obvious.

Amarzguioui indicates that, at the time the invention was made, the art did not disclose, teach, or suggest the claimed combinations of modifications (see, for example, page 593, Discussion), but instead taught that changes to siRNAs had to take target sequences into account:

> On balance, different siRNAs seem to be inactivated by mutations to different degrees, the outcome being at least in part target-sequence dependent.

(Amarzguioui, at page 591, end of first full paragraph). Amarzguioui also discloses that "the existence of different degrees of tolerance for chemical modifications of siRNAs" (Amarzguioui, at page 591, end of first full paragraph), thus suggesting that the suitability of certain chemical modifications for siRNA—and, by implication, combinations of modifications—were not known in the art. However, Amarzguioui discloses neither siRNAs comprising at least one orthoester modified nucleotide, nor siRNAs comprising a lipid conjugate. Further, Amarzguioui contains no teaching, suggestion, or motivation to combine it with any of the cited references to arrive at the rejected claims. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on Amarzguioui, alone or in combination with the other cited references.

Parrish indicates that, at the time the invention was made, the art did not disclose, teach, or suggest the claimed combinations of modifications (see, for example, page 1081, final two paragraphs, to page 1082, final full paragraph), but instead tested only commercially available siRNAs:

> The modifications were chosen based on the commercial availability of nucleoside triphosphates that could be incorporated using T3 or T7 RNA polymerases.

(Parrish at page 1081, last full paragraph). Parrish does not disclose either siRNAs comprising at least one orthoester modified nucleotide, or siRNAs comprising a lipid conjugate. Further, Parrish contains no teaching, suggestion, or motivation to combine it with any of the cited references to arrive at the rejected claims. Indeed, Parrish discloses that certain modifications—and by implication combinations thereof—have unpredictable effects (see, for example, page 1081, second column, first three full paragraphs). Accordingly, Applicants request reconsideration and withdrawal of the rejections based on Parrish, alone or in combination with the other cited references.

Although Scaringe teaches orthoester protecting groups, the Examiner has not indicated where in Scaringe the motivation to combine Scaringe with any of the cited references can be found in order to arrive at the rejected claims. For example, the Examiner has not indicated where in the cited references the motivation can be found to combine an orthoester modification with any of the cited references, where—as illustrated above—the cited references underscore the unpredictability of combinations of modifications. Applicants request reconsideration and withdrawal of the rejections based on Scaringe, alone or in combination with the other cited references.

Although Beigelman purports to disclose what appear to be many thousands of molecules having a modified or unmodified sugar moiety and a modified or unmodified nucleoside base, Beigelman contains no teaching, suggestion, or motivation to arrive at a double stranded polynucleotide comprising at least one 2' orthoester modification and a

conjugate. Applicants submit that Beigelman cannot be fairly read to disclose a double stranded polynucleotide comprising a sense and an antisense strand, wherein the sense and/or antisense strand comprises at least one 2' modified nucleotide and a conjugate (see, for example, Beigelman at page 63, lines 1-3, and formulas 43, 44, 46-52, 58, 61-65, 85-88, 92, 94, and 95), which do not recite 2' modifications in combination with conjugates on a double stranded polynucleotide comprising a sense strand and an antisense strand. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on Beigelman, alone or in combination with the other cited references.

Regarding the Examiner's reliance on Manoharan, Applicants submit that Manoharan discloses oligomers—not double stranded polynucleotides comprising a sense strand and an antisense strand. Also, Applicants submit that Letsinger, also relied upon by the Examiner, merely discloses that a nucleoside can be synthesized that has a cholesteryl moiety attached. Thus, they do not disclose the claimed invention and there is no motivation to combine them with the other references. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on Manoharan and Letsinger, individually or in combination with the other cited references.

Further, Applicants submit that none of the cited references contain any teaching, or suggestion, to employ a double stranded polynucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises at least one orthoester modified nucleotide. Although Scaringe discloses orthoesters, Scaringe does not teach or suggest employing at least one orthoester modification on a sense strand while not on an antisense strand, and therefore Applicants request reconsideration and allowance of at least claims 35, 45, and 62.

Moreover, none of the cited references, alone or in combination, teach or suggest a double stranded polynucleotide comprising at least one orthoester modification on the sense strand only, an antisense strand having at least one 2' modified nucleotide, and a conjugate, wherein the conjugate is located on the sense strand (but not the antisense strand) as recited in claims 49 and 63. Additionally, Applicants submit that none of the

references teach or suggest the composition of claims 49 and 63 wherein the conjugate is a lipid, as recited in amended claims 53 and 67, or cholesterol as cited in claim 68. Accordingly, Applicants request reconsideration and allowance of at least claims 49, 53, 63, 67, and 68.

Finally, Applicants submit that none of the cited references disclose the rejected claims, and that the Examiner has not pointed to where in the cited references the motivation to combine them with one another can be found. Further, Applicants submit that, in light of statements in the cited references regarding unpredictable functional consequences of certain modifications, the cited references do not suggest the present claims. Therefore, a person of ordinary skill in the art would not—without the benefit of the disclosure of the present application in hand—combine the references in a manner so as to arrive at the rejected claims. Accordingly, Applicants request reconsideration and withdrawal of the obviousness rejections.

Conclusion

Reconsideration and allowance are respectfully requested.

No fee is believed to be due with respect to the filing of this Response. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,

Tor Smeland
Registration No.: 43,131
Attorney for Applicants

Kalow & Springut LLP
Telephone No.: (212) 813-1600